Review Article

Expanding Spectrum of Mast Cell Activation Disorders: Monoclonal and Idiopathic Mast Cell Activation Syndromes

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ABSTRACT

Background: In recent years, 2 new syndromes of mast cell activation have been described in patients with episodes of mast cell mediator release that range from flushing and abdominal cramping to anaphylaxis: monoclonal mast cell activation syndrome (MMAS) and idiopathic mast cell activation syndrome (MCAS).

Objective: This review will discuss these 2 new syndromes in the larger context of mast cell activation disorders as well as the diagnostic and treatment approaches for these conditions.

Methods: PubMed was searched using the following terms: *mast cell activation disorder*, *mast cell activation syndrome*, and *clonal mast cell*. Only English-language articles published up until February 27, 2013, were considered.

Results: MMAS has been diagnosed in patients with systemic reactions to hymenoptera stings and elevated baseline serum tryptase as well as in patients with unexplained episodes of anaphylaxis. A bone marrow biopsy establishes the diagnosis by revealing the presence of monoclonal mast cells that carry the D816V *KIT* mutation and/or express CD25 while the diagnostic requirements for systemic mastocytosis are not met. MCAS affects predominantly women in whom no mast cell abnormality or external triggers account for their episodes of mast cell activation. MCAS is a diagnosis of exclusion, and primary and secondary mast cell activation disorders as well as idiopathic anaphylaxis have to be ruled out before making the diagnosis. Patients with MCAS and MMAS are treated in a stepwise fashion with drugs that block the effects of mediators released by mast cells on activation. One third of MCAS patients experience complete resolution of symptoms with treatment, while one third have a major response and one third a minor response to treatment. A combination of drugs is usually necessary to achieve symptom control. No drug trial has been performed in patients with MMAS and MCAS.

Conclusions: MMAS and MCAS are 2 newly described, rare syndromes of mast cell activation. Further studies will be necessary to better understand the cause of these conditions and their natural evolution and to validate and improve the treatment approach. Research should also focus on developing drugs with the potential to cure these debilitating disorders. To achieve these goals, centers with expertise in mast cell activation disorders are essential as they allow for a critical mass of these patients to be enrolled in studies while providing those patients with the most up-to-date diagnostic procedures and treatment strategies. (*Clin Ther*. 2013;35:548–562)

Key words: antihistamine, mast cell activation syndrome, mastocytosis, monoclonal, treatment.

INTRODUCTION

Anaphylaxis is the most dramatic clinical reaction mediated by mast cells. It is characterized by the sudden onset of skin, cardiovascular, respiratory, gastrointestinal (GI), and neuromuscular symptoms and can rapidly lead to death.[1] Although it is widely known that mast cells are activated in the context of an allergic reaction by the allergen-induced cross-linking of surface immunoglobulin (Ig) E/FcεRI (the high-affinity receptor for the Fc region of IgE), it should be rec-

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ognized that many other stimuli and conditions can cause mast cell activation and therefore lead to anaphylaxis.[2] In this regard, 2 *new* syndromes pertaining to mast cell activation have recently been described and deserve special attention: monoclonal and idiopathic mast cell activation syndrome, abbreviated respectively as MMAS and MCAS.

From a clinical standpoint, MMAS and MCAS share many similarities with systemic mastocytosis (SM), a primary disorder of mast cells in which patients experience symptoms ranging from pruritus and flushing to anaphylaxis.[2] SM is caused in >90% of patients by the D816V *c-KIT* gain-of-function somatic mutation.[3,4] The *c-KIT* gene codes for the transmembrane receptor KIT, which transmits signal on engaging its ligand, stem cell factor, and affects growth, differentiation, apoptosis, and activation of mast cells.[5] Therefore, in patients with SM, mast cells are found to be morphologically and functionally abnormal and increased in numbers through clonal expansion.[3] Recently, several groups identified patients with either "idiopathic anaphylaxis" (IA) or systemic reactions to hymenoptera stings in whom mast cells showed clonal abnormalities, alike those seen in SM, but that failed to meet its diagnostic requirements.[6–10] The denomination of MMAS was chosen to characterize this syndrome, which importantly does not appear to simply be an early form of SM.[3,4] In another category of patients with evidence of episodic mast cell activation, investigators have failed to find any mast cell abnormality or external triggers that could explain those episodes.[8,9,11] In 2010, Akin et al[4] proposed diagnostic criteria for this syndrome, which was named *MCAS*. It requires objective evidence of mast cell activation and exclusion of any other known mast cell activation disorder.[4] Its diagnostic criteria have recently been endorsed by an international consensus.[2] This review will discuss these 2 new syndromes, MMAS and MCAS, in the larger context of mast cell activation disorders as well as the diagnostic and treatment approaches for these disorders.

MATERIALS AND METHODS

PubMed was searched using the following terms: *mast cell activation disorder, mast cell activation syndrome,* and *clonal mast cell*. Only English-language articles published up until February 27, 2013, were considered.

RESULTS

Three retrospective cohort studies provided clinical and laboratory data on patients with MCAS, and 1 gave information on their responses to treatment.[8,9,11] Patients with MMAS were described in 5 retrospective studies, which mainly detailed their laboratory features, and none provided data on treatment.[6–10]

Mast Cell Activation Disorders: Diagnostic Criteria and Differential Diagnosis

The clinical features of mast cell activation disorders result from the actions of the various mediators released by mast cells following their activation (**Table I**).[2,12–15] However, none of these are specific for mast cell activation, and many other conditions need to be considered in the differential diagnosis. Therefore, a comprehensive clinical history, physical examination, and basic laboratory tests are crucial in the patient evaluation. Some rather rare diseases and some more common ones deserve special consideration (**Table II**).[16]

Many diseases can cause flushing, which is very common in patients with mast cell activation disorders, and, although accompanying signs and symptoms are helpful in excluding some of them, it is often necessary to order additional tests.[17] Carcinoid tumors release many mediators in an episodic fashion, some of them being also released by mast cells on activation (eg, histamine [H], prostaglandins).[18] This partly explains their similar clinical features (flushing, bronchospasm, diarrhea, hypotension) and that they can both respond to antihistamines.[19] This diagnosis can usually be excluded based on a normal 24-hour urine 5-hydroxyindoleacetic acid level.[18] Whereas the classic triad of headache, sweating, and tachycardia with hypertension readily orients toward a diagnosis of pheochromocytoma, most patients with this condition present with an incomplete triad and with symptoms suggestive of mast cell activation.[20] Measurement of 24-hour urine fractionated metanephrines and catecholamines is a highly sensitive and specific diagnostic test for this disorder.[21] Medullary cancer of the thyroid can cause flushing and diarrhea in patients with advanced disease, at which time they usually also show signs and symptoms of local involvement and have an increased serum calcitonin level.[22]

Patients with postural tachycardia syndrome are frequently young women who experience many symptoms reminiscent of mast cell activation (lightheadedness, fatigue, anxiety, dyspnea, palpitations, and even syncope) on standing.[23] Moreover, superimposed mast

Table I. Mast cell mediator–related symptoms in mast cell activation disorders.

Mediator	Clinical Features
Histamine	Headache, hypotension, pruritus, urticaria, angioedema, diarrhea, anaphylaxis
Tryptase	Bleeding diathesis,*,† inflammation
Chymase‡	Cardiac arrhythmias, myocardial infarction, hypertension
Proteoglycans (heparin)	Bleeding diathesis*
PAF	Abdominal cramping, pulmonary edema, urticaria, bronchoconstriction, hypotension, arrhythmia, anaphylaxis
Prostaglandin D_2	Flushing, mucus secretion, bronchoconstriction, vascular instability, headache, "mixed organic brain syndrome" (poor concentration, memory loss), nausea, abdominal pain
CysLT (LTC_4, LTD_4, and LTE_4)	Mucus secretion, bronchoconstriction, vascular instability
Cytokines (IL-1β, IL-6, TNF-α) and chemokines	Constitutional symptoms (fatigue), inflammation, osteoporosis
Renin[13]	Cardiac arrhythmias, myocardial infarction

CysLT = cysteinyl leukotrienes; IL = interleukin; LTC_4 = leukotriene C_4; LTD_4 = leukotriene D_4; LTE_4 = leukotriene E_4; PAF = platelet activation factor; TNF = tumor necrosis factor.

*Hematoma formation, bruising, prolonged bleeding after biopsies, gingival bleeding, epistaxis, gastrointestinal hemorrhage, conjunctival hemorrhage, or hemorrhagic ulcer disease was observed in 48.5% of patients with a mast cell activation disorder in a cohort of 68 patients.[14]

†Tryptase causes fibrinogen lysis.[15]

‡Chymase induces angiotensin II synthesis.[13]

cell activation has been described in a subgroup of those patients who experience flushing during episodes, as evidenced by elevated urinary methylhistamine levels.[24] Treatment with H_1- and H_2-blockers as well as methyldopa was shown to be beneficial for this particular and rare subgroup, whereas β-blockers caused exacerbations in some of them.[24] This finding highlights the need to differentiate this subgroup with associated mast cell activation from the larger group of patients with POTS who generally benefit from β-blockers and on which antihistamines have no effect.[24]

Respiratory symptoms are rarely predominant in patients with mast cell activation disorders and therefore several other conditions deserve careful consideration in patients with a predominance of those symptoms.[2] In patients with isolated upper respiratory symptoms, direct visualization of the larynx is often key to determine the nature of the obstruction, which can range from vocal cord dysfunction to angioedema. Patients with predominant GI symptoms often need to be evaluated by a gastroenterologist, who can perform endoscopic procedures and biopsies that might be necessary to exclude primary bowel diseases. Finally, psychiatric disorders such as panic attacks should not be overlooked and require psychiatric evaluation after exclusion of all other causes.

To attribute signs and symptoms to a mast cell activation disorder, the following three criteria should be fulfilled, as proposed by an international consensus[2]:

Typical signs and symptoms of mast cell mediator release (affecting at least 2 organ systems)

- Skin: flushing, pruritus, urticaria, angioedema
- Cardiovascular: hypotension
- Respiratory: wheezing, throat swelling
- GI: diarrhea
- Naso-ocular: pruritus

Objective evidence of mediator release

- Elevated serum tryptase: 20% + 2 ng/mL above baseline
- Elevated 24-hour urinary histamine metabolites (methylhistamine)

Table II. Selected differential diagnosis of mast cell activation disorders.

Differential Diagnosis	Useful Test(s) in Investigation
Flushing	
Menopause	FSH, LH, estrogen
Carcinoid syndrome	24-Hour urine 5-hydroxyindoleacteic acid
Pheochromocytoma	24-Hour urine fractionated catecholamines and metanephrines
Medullary carcinoma of the thyroid	Serum calcitonin
Cardiovascular (presyncope/syncope, tachycardia, hypotension)	
Postural tachycardia syndrome (POTS)	Tilt table test
Autonomic dysfunction	Orthostatic drop in blood pressure
Cardiovascular diseases (arrhythmia)	ECG
Respiratory symptoms (throat tightness, stridor, wheezing)	
Asthma	Pulmonary function tests
Vocal cord dysfunction	Laryngoscopy, spirometry
Hereditary and acquired angioedema	C4, C1q, C1 inhibitor antigenic and functional levels
ACE inhibitor–associated angioedema	Plasma bradykinin*
Gastrointestinal symptoms (diarrhea, abdominal cramping)	
Primary bowel disease (irritable bowel syndrome, inflammatory bowel disease)	Endoscopy and biopsy
Neuroendocrine tumors	Serum vasoactive intestinal peptide
Other	
Panic attack	Psychiatric consultation

ACE = angiotensin-converting enzyme; FSH = follicle-stimulating hormone; LH = luteinizing hormone.
*Plasma bradykinin is elevated in ACE inhibitor–associated angioedema and hereditary and acquired angioedema, whereas it is normal in mast cell–related angioedema.[16] Test not currently available. Diagnosis of ACE inhibitor–associated angioedema is based on history.

Elevated 24-hour urinary prostaglandins (prostaglandin D_2; 11β platelet-derived growth factor 2α)

Response to therapy that blocks mast cell mediator activity

H_1-receptor with or without H_2-blockers, ketotifen, cromolyn sodium, aspirin, and leukotriene receptor antagonists

The objective confirmation of mediator release is especially important to avoid misdiagnosing a mast cell activation disorder in patients with nonspecific signs and symptoms.[2,4] Serum tryptase, which is widely available and highly reproducible, is considered the preferred mean to ascertain mast cell activation, with the drawback that its level must be measured between 15 minutes and 4 hours after an event.[2,25] To determine whether a significant increase in tryptase occurred with the symptomatic event, a baseline value has to be measured, usually at least 24 hours after symptom resolution.[2] The increase in tryptase should be of at least 20% + 2 ng/mL above baseline to be considered significant (eg, if baseline is 10 ng/mL, a level $\geq$14 ng/mL would be significant).[2] The baseline

tryptase value can also be used to determine the mast cell burden. Indeed, most patients with SM have a value >20 ng/mL, which is a minor diagnostic criterion of the disease, whereas in MCAS, Hamilton et al[3,11] reported that only 33% of patients had an elevated baseline level (>11.4 ng/mL). In MMAS the value can either be normal or elevated; a mean level of 18.3 ng/mL was reported in 1 cohort.[9] Other less well-validated methods of documenting mast cell activation include measurement of 24-hour urine methylhistamine or prostaglandins (prostaglandin D_2 or 11β platelet-derived growth factor 2α), although the significant level of increase for those markers has not been established.[2,26,27] On the other hand, the baseline levels were found to be elevated in a majority of patients with MCAS, although very few patients had baseline elevations in >1 mediator.[11] Finally, it is important to document clinical improvement with antimediator therapy, particularly antihistamines or other mast cell stabilizing agents such as cromolyn sodium or ketotifen.[2] Also, some patients may respond only if drugs such as aspirin or leukotriene antagonists are added, which may relate to the predominant mediator released by their mast cells on activation.[28]

Mast Cell Activation Disorders: Classification and Diagnostic Approach

With improvements in the understanding of mast cell activation disorders, it has become useful to classify them into 3 distinct categories: primary, secondary, and idiopathic, as follows[2,4]:

Primary

- Cutaneous mastocytosis (urticaria pigmentosa, diffuse, telangiectasia macularis eruptiva perstans)
- Systemic mastocytosis (indolent, aggressive, associated with a hematologic non–mast cell lineage disease, mast cell leukemia)
- Mast cell sarcoma
- Mastocytoma
- MMAS

Secondary

- IgE-mediated hypersensitivity reactions (eg, food, insect, drug-induced anaphylaxis)
- Drugs (eg, vancomycin, opioids, taxanes)
- Mast cell hyperplasia (associated with chronic infections, neoplasia, and autoimmune conditions, possibly due to an excess of stem cell factor; these reactive states are infrequently the cause of mast cell activation disorders[2])

Idiopathic

- IA
- MCAS

Secondary causes of mast cell activation should be sought in every patient because they may coexist with primary and idiopathic disorders.[2] For instance, it is not unusual to find a history of systemic reaction to hymenoptera stings in patients with SM, MMAS, or even MCAS.[7–9] Also, it is important to consider unusual allergens, such as alpha-gal, which causes delayed IgE-mediated reactions to mammalian meat, before concluding to an idiopathic disorder.[29]

A primary mast cell disorder should be suspected in any patient presenting with a systemic reaction to hymenoptera stings or episodes of mast cell activation either without an identifiable trigger or with multiple unrelated triggers, especially if associated with hypotension and if urticaria or angioedema is absent.[2,3,7,9,17] As a first step, a baseline serum tryptase level should be measured because an increased level (>11.4 ng/mL) would favor the presence of a primary disorder.[2,8] Then, depending on the clinical features and the tryptase level, a bone marrow biopsy should be performed to allow the diagnosis of a primary mast cell disorder. A baseline tryptase level >20 ng/mL, episodes of unexplained anaphylaxis, and the presence of urticaria pigmentosa (the most common form of cutaneous mastocytosis) in adults are generally considered indications for bone marrow biopsy.[17] Also, abnormalities on complete blood count in patients with a mast cell activation disorder should lead to a bone marrow biopsy because several hematologic non–mast cell lineage disorders can be associated with SM (SM-AHNMD [SM associated with a hematologic non–mast cell lineage disease]). These patients usually have cytopenias or thrombocytosis and/or leukocytosis on complete blood count, are male, have fewer skin symptoms, and are older than patients with pure SM.[30] The most commonly associated hematologic diseases are chronic myelomonocytic leukemia and myelodysplastic syndrome (60%), but other myeloproliferative neoplasms and lymphoproliferative diseases have also been described.[30] Finally, the presence of unexplained osteoporosis, hepatomegaly, or splenomegaly in pa-

tients with a mast cell activation disorder should raise suspicion for an aggressive variant of SM and therefore justifies a bone marrow biopsy.[3]

SM is diagnosed, according to the following World Health Organization criteria, as the presence of either the major criterion listed subsequently and at least 1 of the 4 minor criteria, or at least 3 minor criteria if the major criterion is not met[31]:

Major criterion

- Multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s)

Minor criteria

- In biopsy sections of bone marrow or other extracutaneous organs, >25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology, or, of all mast cells in bone marrow aspirate smears, >25% are immature or atypical
- Detection of an activating point mutation at codon 816 of *KIT* in bone marrow, blood, or other extracutaneous organ
- Mast cells in bone marrow, blood, or other extracutaneous organ express CD2 and/or CD25 in addition to normal mast cell markers
- Serum total tryptase persistently exceeds 20 ng/mL (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid)

These criteria encompass the diverse mast cell abnormalities that are thought to result from an exon 17 *KIT* mutation (D816V in >90%), which drives the clonal expansion of bone marrow mast cells.[31] Additionally, 4 categories of SM have been described: indolent SM (ISM), aggressive SM (ASM), SM-AHNMD, and mast cell leukemia (MCL).[3] These are usually distinguished based on bone marrow biopsy findings and associated organ involvement (eg, liver failure, hypersplenism, cytopenias, bone lesions).[3] Patients with more aggressive forms of SM (ASM and MCL) carry the D816V *KIT* mutation in cells from other myeloid lineages and even hematopoietic stem cells in contrast to patients with ISM or MMAS, in whom the mutation is found only in the mast cell lineage.[32]

MMAS is diagnosed based on the presence of clonal mast cells in the bone marrow specimens of patients who do not meet the diagnostic criteria of SM (fulfilling only 1 or 2 minor criteria).[3] Clonality is usually revealed by the presence of the D816V *KIT* mutation and aberrant expression of CD25 on bone marrow mast cells.[3] Two independent groups first described patients with this condition in 2007,[6,10] and a few more have been reported since.[7–9] In a case reported by Sonneck et al,[10] the patient presented with a history of systemic reaction to hymenoptera stings and had an elevated baseline serum tryptase (12 ng/mL), whereas in the case series by Akin et al,[6] patients had episodes of IA. In both studies, *KIT* mutations could not be found on unsorted bone marrow samples, although all patients had bone marrow mast cells with an aberrant morphology (spindle shaped) and CD25 expression.[6,10] In 2009, Bonadonna et al[7] reported 9 patients with MMAS diagnosed following a systemic reaction to hymenoptera stings and the finding of elevated baseline serum tryptase. Two patients had the D816V *KIT* mutation, 1 had a D816H *KIT* mutation, and no mutations were found in the remainder.[7] Also, in 2 patients with a *KIT* mutation, aberrant CD25 expression was not detected.[7] Alvarez-Twose et al[8] mentioned 3 patients with MMAS (with a *KIT* mutation and aberrant CD25 expression) in a 2010 study, although patients with aberrant CD25 expression in the absence of a *KIT* mutation or vice versa were excluded. In 2012, Alvarez-Twose et al[9] reported 11 patients with *KIT* mutations in bone marrow mast cells, and only 4 of those had aberrant CD25 expression. Almost half of cases (45.5%) had a history of systemic reaction to hymenoptera stings and 54.5% had an episode of syncope. Given the rarity of this syndrome and the bone marrow mast cell–enrichment techniques often necessary for its diagnosis (due to the low number of abnormal mast cells), referral of patients in whom this condition is suspected to centers with expertise in mastocytosis is strongly encouraged.

Cutaneous mastocytosis (CM) is a primary mast cell disorder in which the skin is the only organ affected by abnormal mast cells that have been found to also carry *KIT* mutations.[33] Several forms of cutaneous disease have been described, but urticaria pigmentosa is by far the most common.[34] In children, cutaneous mastocytosis is rarely associated with systemic disease and therefore a bone marrow biopsy is unwarranted.[34] Importantly, despite the absence of systemic disease, the local release of mediators from skin mast cells is sufficient to cause systemic symptoms of mediator release, and such an occurrence should not be misinterpreted as a sign of systemic disease.[34] Also, the vast majority of

children will undergo spontaneous resolution of CM before puberty, although in a cohort of 50 children with CM, 42% carried an exon 17 *KIT* mutation.[33,34] In contrast, most adults with CM have an underlying SM and should undergo a bone marrow biopsy regardless of the presence of associated systemic symptoms of mediator release.[17] Conversely, 80% of SM patients have cutaneous disease that manifests as urticaria pigmentosa.[4] In contrast, patients with MMAS and MCAS never have CM, and patients with ASM or MCL frequently lack CM.[35]

Finally, there remains a category of patients in whom no mast cell abnormality can be identified and no secondary cause can be found to account for their episodes of mast cell activation. This disorder has been termed *MCAS,* and its diagnostic criteria include those of any mast cell activation disorder with the additional requirement that primary, secondary, and other well-defined idiopathic mast cell activation disorders be ruled out first.[4] Importantly, these patients should not meet the diagnostic criteria for IA although they might experience IA from time to time. In that case, these patients should be referred to as *MCAS with IA*.[4,17] Alvarez-Twose et al[8] described 32 patients with this syndrome in 2010, of whom 69% were women. They were compared with a cohort of 48 patients with ISM without cutaneous disease. It was found that a higher baseline serum tryptase (>25 ng/mL), male sex, the presence of hypotensive episodes, and the absence of urticaria and angioedema favored a clonal mast cell disorder (eg, ISM).[8] A clinical score derived from these characteristics was validated in another study in which it was found to be a more accurate predictor of clonal mast cell disorder compared with baseline serum tryptase level alone.[9] In 2011, Hamilton et al[11] reported on 18 patients with MCAS, of whom 16 were women. Their most common symptom was abdominal pain, a minority (17%) had had anaphylaxis, and their mean baseline serum tryptase was 10.7 ng/mL, providing support for the differentiating clinical characteristics proposed by Alvarez-Twose et al.[8] **Table III** delineates the distinctive features of SM, MMAS, MCAS, and IA, and the **Figure** provides a diagnostic algorithm to mast cell activation disorders.

Treatment of MMAS and MCAS

Treatment of patients with MMAS and MCAS is aimed at mitigating the effects of mediators released by mast cells on activation and to a certain extent at preventing mediator release. Unfortunately, no curative therapy exists for these

Table III. Comparison of SM, MMAS, MCAS, and IA.

Clinical and Laboratory Features	SM	MMAS	MCAS	IA
Multifocal mast cell aggregates	Present*	Absent	Absent	Absent
D816V *KIT* mutation	Present†	Present‡	Absent	Absent
Aberrant CD25 expression on bone marrow mast cells	Present	Present‡	Absent	Absent
Baseline tryptase	Elevated§	Normal or elevated	Normal or elevated	Normal
Baseline 24-hour urine methylhistamine or Prostaglandin D_2/11β-$PGF_{2\alpha}$	Elevated	Normal or elevated	Normal or elevated	Normal
Urticaria pigmentosa	Present or absent	Absent	Absent	Absent
Mediator release symptoms	Present	Present	Present	Present
Response to antimediator therapy	Good	Good	Good	Variable

Adapted with permission from J Allergy Clin Immunol.[4]
IA = idiopathic anaphylaxis; MCAS = idiopathic mast cell activation syndrome; MMAS = monoclonal mast cell activation syndrome; PGF = platelet-derived growth factor; SM = systemic mastocytosis.
*Major diagnostic criterion for SM; not present in all patients with SM.
†Other *KIT* mutations have also been associated with SM.
‡May require enrichment of bone marrow mast cells.
§Serum tryptase >20 ng/mL is a minor criterion for SM; not present in all patients with SM.

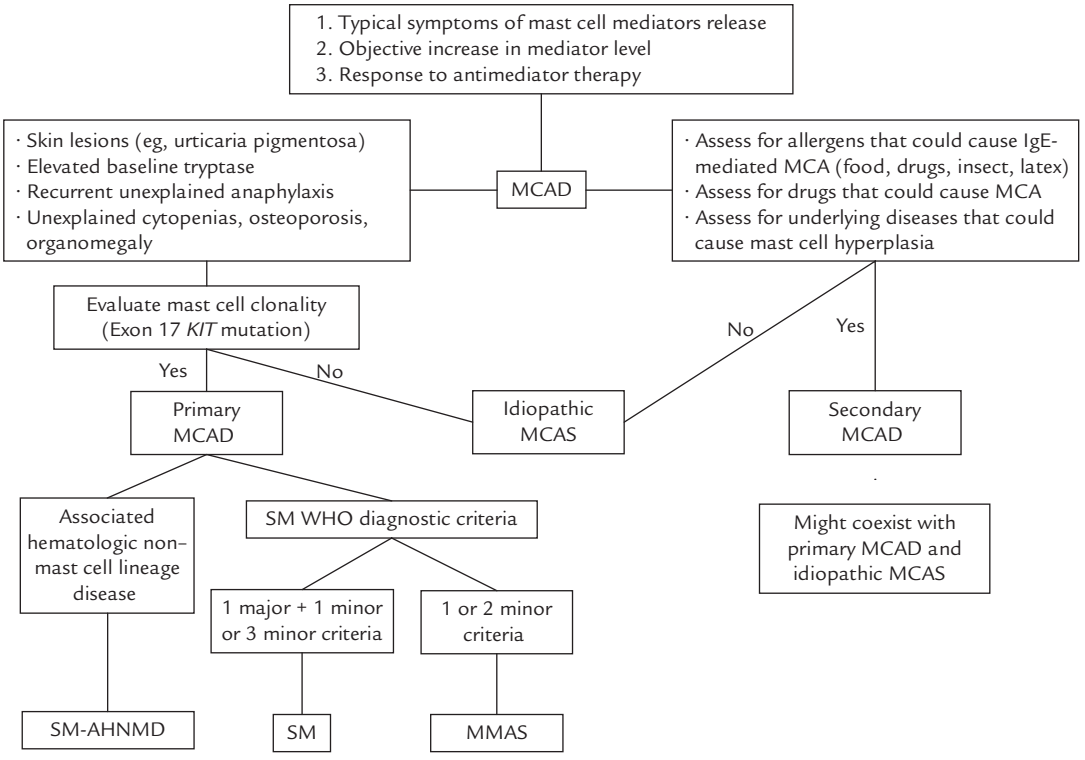

Figure. Diagnostic algorithm for mast cell activation disorders. AHNMD = associated hematologic non–mast cell lineage disease; MCA = mast cell activation; MCAD = mast cell activation disorder; MCAS = mast cell activation syndrome; MMAS = monoclonal mast cell activation syndrome; SM = systemic mastocytosis.

conditions at the present time. Therefore, the aim of treatment is to achieve symptom control so as to normalize quality of life. Few patient cohorts with these diseases have been described to date and thus the prophylactic treatment regimen is largely based on the one used in patients with SM for which a larger body of evidence is available.[3] The treatment approach is stepwise, usually starting with a combination of H_1-receptor and H_2-receptor blockers, with adjustments according to symptoms and response to treatment (**Table IV**). In patients with MCAS the rate of response to antimediator therapy is rather good, with 33% showing complete response, 33% a major response, and 33% a minor response after 1 year of treatment.[11] Also, symptoms may not be equally responsive to treatment, as shown in **Table V**.[11] No data on the response to treatment in MMAS patients were found.

Trigger Avoidance

Identification and avoidance of relevant triggers of mast cell activation in a particular patient is of prime importance for symptom control:

- Alcohol (estimated prevalence in MCAS patients, 67%[11])
- Heat (estimated prevalence in MCAS patients, 50%[11])
- Drugs (estimated prevalences in MCAS and MMAS patients, 30.8% and 36.4%, respectively[9])
  - Antibiotics
  - NSAIDs
  - Narcotics
  - Neuromuscular blocking agents
- Radiocontrast media
- Invasive procedures (eg, general anesthesia, biopsy, endoscopy)
- Hymenoptera stings (estimated prevalences in MCAS and MMAS patients, 21.2% and 45.5%[9])
- Fever or infection
- Exercise
- Physical stimuli (eg, pressure, friction)

Table IV. Stepwise prophylactic treatment approach for patients with MCAS and MMAS.

System/Symptoms/Step No.	Drugs
Skin	
Pruritus, flushing, urticaria, angioedema, dermatographism	
1	H_1-blockers* ± H_2-blockers
2	Leukotriene antagonists[†]
3	Aspirin[‡]
4	Ketotifen
Gastrointestinal	
Diarrhea, abdominal cramping, nausea, vomiting	
1	H_2-blockers
2	Cromolyn sodium
3	Proton pomp inhibitors
4	Leukotriene antagonists[†]
5	Ketotifen
Neurologic	
Headache, poor concentration and memory, brain fog	
1	H_1- and H_2-blockers
2	Cromolyn sodium
3	Ketotifen
Cardiovascular	
Pre-syncope, syncope, tachycardia	
1	H_1- and H_2-blockers
2	Corticosteroids[§]
3	Omalizumab[‖]
Pulmonary	
Wheezing, throat swelling	
1	H_1- and H_2-blockers
2	Leukotriene antagonists[†]
3	Corticosteroids (including inhaled corticosteroids)[§]
4	Omalizumab[‖]
Anaphylaxis	
Acute	Epinephrine (intramuscular)
1	H_1- and H_2-blockers
2	Corticosteroids[§]
3	Omalizumab[‖]
Naso-ocular	
Nasal stuffiness, nasal pruritus, conjunctival injection	
1	H_1-blockers (including topical formulations)
2	Topical corticosteroids
3	Cromolyn sodium (topical formulation)

*Nonsedating second-generation H_1-blockers preferred.
[†]Montelukast, zafirlukast, or zileuton.
[‡]Especially useful in patients with treatment-resistant flushing and elevated urinary prostaglandin D_2.
[§]Suggested initial dose of 0.5 mg/kg/d tapered over 1 to 3 months.
[‖]For recurrent anaphylactic episodes (≥1/mo) unresponsive to corticosteroids or dependent on corticosteroids for control.

Table V. Response to treatment in MCAS patients.

Symptom	Response Rate, %
Abdominal pain	82
Headache	80
Diarrhea	75
Poor concentration and memory	58
Flushing	38

Created with data from reference 11.

Emotions/stress
NSAIDs

In patients with MCAS, alcohol and heat are the most common triggers of symptoms.[11] Hymenoptera stings are also frequently reported as triggers in MMAS and MCAS and, importantly, can be the sole manifestation of the disease.[9] Those patients should be thoroughly investigated for the presence of venom-specific IgEs and if present should be offered venom immunotherapy (VIT).[7,9,36,37] Indeed, patients with clonal mast cell disorders, mainly SM, and hymenoptera venom allergy are at high risk for anaphylaxis from a recurrent sting, and VIT has been shown to reduce that risk to ~25%.[38] However, the buildup phase of VIT can also induce systemic reactions, particularly in patients with elevated baseline serum tryptase concentration.[38,39] Therefore, it should be done under close supervision and under the cover of premedication with antihistamines and, in some cases, omalizumab.[37,40] Finally, as patient fatalities have been reported following discontinuation of VIT after the usual 3- to 5-year duration, it is now recommended to give VIT for the patient's lifetime in those with an elevated baseline serum tryptase level.[37]

Other preventable triggers of mast cell activation include invasive medical procedures, such as general anesthesia and radiologic procedures with contrast media.[17] Premedication is usually recommended in patients with SM and consists of H_1- and H_2-blockers, to which leukotriene antagonists and corticosteroids can be added, depending on the severity of the underlying disorder and previous reactions to such triggers.[3] Although data are lacking and few patients with MMAS and MCAS seem to experience adverse outcomes with those interventions, it is practice to use premedication in those patients as well.[41]

Treatment of Acute Episodes

Patients with MCAS and MMAS and a history of anaphylaxis and those with an elevated baseline serum tryptase concentration (>11.4 ng/mL) should carry 2 doses of epinephrine in autoinjectors at all times because mast cell mediator release is unpredictable and could be life-threatening.[3,42,43] Epinephrine should be administered without delay intramuscularly in the thigh, with the patient in the recumbent position, in the context of an episode of mediator release with associated hypotension or respiratory compromise.[1] Fluid resuscitation is also important in patients with anaphylaxis.[1] Other symptoms are usually managed with H_1- and H_2-blockers, and β-agonists may also be necessary for treating bronchospasm, although none of these treatments should be used as a substitute for epinephrine in the event of anaphylaxis.[1] Corticosteroids (0.5–1 mg/kg) should be considered to prevent delayed and recurrent symptoms of anaphylaxis.[1]

Prophylaxis

Antihistamines

Histamine is involved in a wide array of mast cell activation manifestations, and its blockade is thus of prime importance for adequate symptom control.[2,3] Histamine exerts its effects through 4 different receptors, although H_1- and H_2-receptors seem to be the most relevant ones in patients with mast cell activation disorders.[44] Therefore, the use of H_1- and H_2-blockers is considered the starting point in any patient with MMAS or MCAS.[3,11,17] H_1-blockers have been shown to be effective in controlling skin symptoms, tachycardia, and abdominal cramping in SM.[45,46] Nonsedating H_1-blockers (cetirizine, fexofenadine) are preferred over older sedating ones (diphenhydramine, hydroxyzine, doxepin).[45] The dose of these agents can be doubled to achieve symptom control similar to what is done in patients with chronic urticaria.[3,11,17,45] In the same manner, a combination of H_1-blockers can also be used, although side effects should be monitored.[45] Ketotifen (available in Europe and Canada), which, in addition to acting as an H_1-blocker, has mast cell–stabilizing properties can also be used; it is mainly effective against skin symptoms in SM.[45,47,48]

H_2-blockers are often added to H_1-blockers to optimize symptom control.[34,45,49–51] In addition, H_2-

blockers are used to block the gastric hypersecretion found in patients with mast cell activation disorders and to relieve the associated GI symptoms.[51,52] Proton pump inhibitors are also useful in treating refractory GI symptoms.[45] Oral cromolyn sodium has been shown in small placebo-controlled trials to be particularly useful in the control of GI symptoms in SM,[50,53,54] and its efficacy has also been shown for neurologic ("mixed organic brain syndrome") and skin symptoms in some patients with SM.[53] Its mechanism of action could involve the inhibition of mast cell mediator release, although cromolyn has been found to be a weak inhibitor in that regard and to have no inhibitory effect on skin mast cells.[55,56] Recent data suggest that its effect on pruritus might be mediated by the inhibition of C-fiber sensory nerves rather than through mast cell inhibition.[57]

Leukotriene Antagonists

Because cysteinyl leukotrienes mediate many signs and symptoms of mast cell activation, their blockade could in theory be beneficial. Indeed, case reports have shown a positive impact of the cysteinyl leukotriene 1 receptor blocker montelukast on wheezing and on GI and skin symptoms in pediatric patients with mastocytosis.[58–60] These patients had refractory symptoms despite treatment with H_1- and H_2-blockers, cromolyn sodium, and corticosteroids.[58,59] Montelukast helped to reduce the corticosteroid dose in 1 case.[58]

Aspirin

Prostaglandins are overproduced in many patients with mastocytosis and also in patients with MMAS and MCAS.[2,11,28] Therefore, by using the NSAID aspirin, which inhibits cyclooxygenase, prostaglandin generation could in theory be decreased, which would in turn lead to symptom improvement.[45] However, whereas some patients benefit from this therapy, especially for refractory flushing, some experience hypersensitivity reactions.[28,61,62] Therefore, before giving aspirin to a patient with MMAS or MCAS, a drug challenge should be performed to ensure tolerance unless the patient has a recent record of tolerating NSAIDs.[45] Butterfield et al[28] described 4 patients with a likely diagnosis of MCAS characterized by overproduction of prostaglandins but not histamine. Interestingly, they all responded well to treatment with aspirin, whereas they were all refractory to antihistamines.

Omalizumab

Omalizumab, a humanized monoclonal antibody that binds free IgE, has been used with success in several cases of mast cell activation disorders refractory to maximal antihistamine doses and requiring corticosteroids for symptom control.[63,64] Those patients also experienced recurrent episodes of anaphylaxis. With omalizumab treatment, patients showed a marked reduction in symptoms and anaphylactic episodes, allowing a reduction in concurrent medication use.[63,64] Effect seemed to manifest after ~6 months of treatment and was likely related to the mast cell–stabilizing properties of omalizumab.[64,65] To the contrary, in another patient, mast cell activation symptoms followed the injections of omalizumab and led to its withdrawal.[64] In the same report, 2 cases of SM also showed benefit with omalizumab in symptoms and medication use.[64]

Other Therapies

MCAS and MMAS are benign diseases and therefore those patients are not candidates for treatment with tyrosine kinase inhibitors (TKIs) or cytoreductive therapies used in patients with smoldering ISM, ASM, or MCL.[3,17] However, because patients with MMAS have a clonal mast cell disorder, they need to be monitored for the development of complications associated with advanced forms of SM, such as osteoporosis, bone lesions, hepatomegaly, splenomegaly, and cytopenias.[3]

TKIs are a promising drug class for the treatment of patients with advanced forms of SM because they specifically target KIT.[66] However, most TKIs, including imatinib, are ineffective against the D816V *KIT* mutation, which affects >90% of patients with SM.[66] Nonetheless, a newer TKI, midostaurin, has shown promising efficacy and tolerability results in patients with the D816V *KIT* mutation.[66] Although investigational at the present time, TKIs could be used in the future for patients with MMAS with complications such as bone loss or recurrent anaphylaxis. New drugs are also being developed that inhibit mast cell activation. As such, quercetin, a flavonoid, has been shown to block in vitro the mast cell release of histamine, prostaglandins, leukotrienes, tryptase, and inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α, although its efficacy in mast cell activation disorders remains to be validated in clinical trials.[56,67]

CONCLUSIONS

MMAS and MCAS are new and rare diseases for which much remains to be learned about natural evolution, prognosis, and pathophysiology. Their clinical presentation, with its wide array of unspecific signs and symptoms, requires a high degree of suspicion to avoid delays in diagnosis and treatment, which are currently fairly common. It is therefore crucial to increase awareness of these syndromes in the medical community.

A diagnosis of mast cell activation disorder should strictly abide by the recently established diagnostic criteria, which require that the patient present typical signs and symptoms, that objective evidence of mediator release be documented, and that a response to antimediator therapy be observed. It should also be made after consideration of the relevant differential diagnosis. Differentiation between the diverse primary mast cell disorders (eg, SM, MMAS) and between secondary and idiopathic (eg, MCAS) disorders requires a certain level of expertise and, in some instances, access to techniques that are not widely available at this time. Therefore, referral to a center specialized in mast cell activation disorders is encouraged to ensure proper diagnosis and optimal treatment of these patients.

Bone marrow biopsy is crucial to verify the presence of clonal mast cells, which indicate a primary mast cell disorder. Clonality is usually established by detection of an exon 17 *KIT* mutation (most commonly D816V) in bone marrow mast cells. It is also suggested by an aberrant expression of CD25 by these cells. These anomalies are found in patients with MMAS who, on the other hand, do not fulfill the diagnostic requirements for SM. In contrast, MCAS is a diagnosis of exclusion in which no mast cell anomaly or secondary disorders account for the mast cell activation disorder.

The therapeutic approach for MMAS and MCAS, in the absence of drug efficacy trials, is largely based on symptoms and tailored to the patient's response. All patients must be carefully evaluated to determine their specific risk for anaphylaxis and the need to carry 2 epinephrine autoinjectors. Prophylactic therapy usually consists of a combination of several mediator antagonists. Also, patients with hymenoptera venom allergy should be treated with lifelong VIT. For refractory cases, the use of omalizumab has been reported to be useful and is worth considering. Finally, it is still necessary to define whether and when patients with MMAS might be candidates for TKIs, as promising as they may seem for mastocytosis.

Research on these new syndromes is thus essential, and centers with expertise in mast cell activation disorders are key in this regard because they allow for a critical mass of these patients to be enrolled in studies while providing those patients with the most up-to-date diagnostic procedures and treatment strategies.

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CONFLICTS OF INTEREST

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